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Overcoming severe adverse reactions to venom immunotherapy by using anti-IgE antibodies in combination with a high maintenance dose

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Abstract:

Background: An omalizumab treatment and a high maintenance venom dose may both help to prevent recurrent systemic allergic reactions (SAR) to venom immunotherapy (VIT). The effectiveness of this combination therapy, however, is unclear.

Objective: We wanted to explore the possibility whether a temporary treatment with the anti-IgE antibody omalizumab, combined with a VIT using an elevated maintenance dose of >100 µg venom may establish a permanent tolerance of maintenance VIT.

Methods: For this retrospective case series, we scoured our institutional data base for patients who had had an insect venom allergy, and in whom it had not been possible to continue VIT because of repeated unstoppable SAR during maintenance VIT. Patients were divided into those who had received the combination therapy (omalizumab group), and those who had not received omalizumab because its costs could not be covered (controls). Guided by the total IgE level and by body weight, omalizumab had been given subcutaneously 5, 3 and 1 week before VIT had been restarted. Three to six months after an elevated maintenance dose (200 – 300 µg venom) had been reached, omalizumab had been stopped.

Results: Between 2006 and 2011 15 patients had qualified for an off-label use of omalizumab. 10 patients had received the combination therapy, five patients had remained without such a therapy. The combination therapy lead to a durable tolerance of VIT in all patients even after omalizumab had been discontinued (median of follow-up time 5.8 years, IQR 2.7-8.6 years). Sting challenge tests were tolerated by all of the re-stung omalizumab patients (n=8). In all controls VIT had to be stopped permanently due to repeated SARs (p<0.001 vs. omalizumab group).

Conclusions: Combining a temporary omalizumab therapy with an elevated maintenance dose seems a promising approach to achieve a tolerance of treatment in patients with a recurrent SAR to VIT.

Introduction

Venom immunotherapy (VIT) is an established treatment for patients with a sting-induced anaphylaxis caused by venom-specific IgE antibodies. Following VIT, more than 93% of all patients are protected against subsequent systemic allergic reactions due to stings by the culprit insect (1, 2). Risk factors associated with VIT failure are bee venom allergy, an elevated serum tryptase concentration, mastocytosis, systemic side effects during VIT, and ACE inhibitor treatment (2).

VIT itself may cause systemic allergic reactions. The reported frequencies of systemic allergic reactions during the build-up phase of VIT range between ca. 10% (3, 4) and 20% (5). The incidence of severe VIT-related side effects peaks during the build-up phase and declines subsequently (3, 5). The majority of these reactions are usually mild and non-recurring (5). However, some of these systemic reactions may lead to respiratory and/or cardiovascular dysfunction, requiring emergency interventions and possibly an early treatment stop.

Stopping VIT in patients with repeated anaphylactic reactions to VIT is controversial because these patients are at a particularly high risk for future anaphylactic reactions to Hymenoptera stings. Avoidance of any re-stings is essential for those patients since they may sustain very severe sting reactions resulting in disablement or death. Under such circumstances, it may be necessary for them to change their profession and to refrain from many private out-door activities causing a significant loss of quality of life. To improve the quality of life in these particular patients, special treatment concepts are required ideally resulting in a life-long tolerance of stings from the culprit insect species.

Before definitively stopping VIT several actions can be taken to establish a treatment tolerance while being on a standard maintenance dose: ACE-inhibitors should be discontinued (2), and it may be advantageous to use a slower build-up protocol when restarting VIT. Sometimes, the switch from a slow to a fast build-up protocol may improve the tolerance (6). Furthermore, doctors may switch to a purified depot preparation (7, 8) possibly evoking less systemic allergic side effects. Concomitant treatment with H1-antihistamines may attenuate mild systemic allergic reactions (affecting only the skin) due to VIT (9, 10). If systemic allergic reactions during VIT cannot be eliminated by standard measures, omalizumab therapy presents another

alternative to enable a continuation of VIT. Omalizumab is a humanized, monoclonal anti-IgE antibody, which was originally approved for the treatment of allergic asthma; since 2014 it is licensed for the treatment of chronic spontaneous urticaria. The effectiveness of omalizumab for improving VIT tolerance, however, is unclear (11, 12). The current retrospective case series tried to explore the possibility whether a combination therapy (omalizumab + high maintenance dose of venom) might represent such a special treatment concept possibly inducing tolerance of VIT in patients with unstoppable SARs due to VIT.

Patients and Methods

For this retrospective case series, we conducted a search for patients treated in our institution who had developed repeated moderate to severe systemic allergic reactions to VIT, in whom VIT had already been stopped or was about to be stopped because of those reactions, and who had qualified for treatment with omalizumab between July 2006 and 2011. Criteria for an off-label use of omalizumab had been a) the ineffectiveness of antihistamines to prevent systemic reactions, b) a particularly high individual risk of severe sting anaphylaxis due to intense exposure, c) a history of severe sting reactions with loss of consciousness ($\geq$ severity grade III according to Ring and Messmer [13], Table 1), or d) mastocytosis as an underlying disease. SARs were treated according to current guidelines. Written informed consent for an off-label omalizumab use had been obtained from all patients scheduled to be treated with omalizumab. The local institutional review board had no objection to an anonymous retrospective review of the notes of the patients.

Data of standardized routine procedures, which had been used for clinical diagnostics and treatment, were collected from the patient records. Insect sting history, gender, age and the type of medication were recorded. The definition of the severity grade of field sting reactions referred to that sting, which had resulted in the hitherto most severe systemic reaction. We also documented several variables such as baseline tryptase concentration, concentrations of venom-specific IgE antibodies (both ImmunoCAP Phadia, Uppsala, Sweden), and skin test reactions to honeybee

and *Vespula* venom (ALK-Abelló, Hørsholm, Denmark). Concentrations and reactions had all been measured at the time of the first visit in our outpatient clinic.

In three patients a basophil activation test (BASOTEST®, Orpegen Pharma, Heidelberg, Germany) had been performed according to the manufacturer's instructions. Heparinized full blood had successively been pre-incubated with IL-3, with a washing buffer (negative control), with fMLP (positive control), or with Hymenoptera venom (bee venom, 1 µg/ml, Reless Bienengift®, or *Vespula* venom, 1 µg/ml, Reless Wespengift®, ALK Abelló). Basophil activation had been assessed by CD63 expression measured on the surface of basophils via flow cytometry (BD FACScan).

After VIT had been stopped or had been modified by a dose reduction, treatment was restarted after pre-treatment with anti-IgE-antibodies. The dosage of omalizumab (Xolair®, Novartis) was given according to the manufacturers instruction for treatment of patients with asthma, e.g., 150 mg for patients with a total IgE < 100 kU/l and a body weight of less than 70 kg. Omalizumab was administered by subcutaneous injections five, three and one week before restarting the build-up of VIT. Build-up of VIT was performed by a rush (Table 2a) or an ultra-rush protocol (Table 2b). For the build-up we used ALK-lyophilisiert SQ® (equal to Aquagen®, ALK-Abelló) or VENOMENHAL®: (HAL Allergy, Leiden, Netherlands) and for the maintenance treatment ALK-lyophilisiert SQ® and/or ALK-depot SQ® (equal to Alutard®, ALK-Abelló) or VENOMENHAL®. After the elevated maintenance dose (200 – 300 µg venom) had been reached, omalizumab was administered every four weeks. Omalizumab was stopped three to six months later. A sting challenge test was recommended to those patients who were on the intended maintenance dose without showing side effects.

Results

Patient characteristics

Between 2006 and 2011 15 patients (29 – 65 years old, 7 males) could be identified in whom antihistamines and preliminary dose reduction had not been effective to establish tolerance of standard maintenance treatment. The standard maintenance dose had been 100 µg; for patients with a bee venom allergy and with particular risk factors, we had used 200 µg from the beginning of the maintenance phase. Patients diagnosed with a double venom allergy also had a VIT with the respective complementary venom. In about half of the patients repeated systemic allergic reactions developed shortly after the beginning of the build-up phase; three patients had systemic reactions upon VIT after a systemic reaction at a sting challenge; three other patients developed systemic reactions after an infection or a vaccination, respectively. One patient (Nr. 10) was suffering from allergic rhinitis and asthma due to pollen allergy; she had many mild systemic reactions during maintenance VIT; in this patient severity of systemic reactions tended to increase during the pollen season.

After the onset of repeated side effects, either VIT had been stopped, or the patients or treating physicians, respectively, were about to stop VIT. Insurance companies agreed to cover costs for an off-label omalizumab therapy in eight patients, but did not do so in seven. Two of the latter patients paid for the drug themselves forming an omalizumab group of 10 patients and a control group of five patients.

The clinical data of the omalizumab patients are shown in Table 3. Nine patients presented with a history of a severe reaction prior to VIT (anaphylactic shock with loss of consciousness), and five patients were suffering from mastocytosis. One patient had a predominant out-door occupation, another patient, who was allergic to bee-venom, had bee-keepers as family members; two patients had a variable occupational exposure to insects. All occupationally exposed patients had to consider a professional change if VIT had to be stopped definitively. Three patients

were intensely practising outdoor activities such as riding horses or driving bicycle. All patients reported a significant loss of quality of life resulting from their unsuccessful therapy of venom allergy. Six patients experienced mild to moderate systemic allergic reactions during the initial build-up; finally, however, these patients successfully reached the maintenance dose.

The clinical data of the control patients are shown in Table 4. All patients presented with a history of a severe reaction prior to VIT (anaphylactic shock with loss of consciousness), and were suffering from mastocytosis. All patients were allergic to bee venom, and one patient additionally had a vespula venom allergy. Control patients did not differ significantly from omalizumab patients with regard to age (median 49 years, IQR 41-54 years, $p=0.371$ [Mann-Whitney U-test] vs. 40 years, IQR 34-53 years), baseline tryptase concentration (median 21.8 $\mu\text{g/ml}$, IQR 15.7-52.3 $\mu\text{g/ml}$, $p=0.206$ vs. 14.8 $\mu\text{g/ml}$, IQR 6.6-26.7 $\mu\text{g/ml}$), gender distribution ($p=1.000$, Fischer's exact test), or type of VIT causing side effects ($p=0.524$).

Treatment effects

In all control patients VIT had to be stopped definitively due to repeated unstoppable SARs (Table 4). In all patients pre-treated with omalizumab (Table 3) VIT was restarted with a rush (patients Nr. 2-8 and 10) or an ultra-rush protocol (patients Nr. 1 and 9) either de novo or with the last venom dose which had been tolerated by the patient. All patients received antihistamines during build-up. The intended new maintenance dose exceeded that, which had not been tolerated before, by 100 μg . Three patients received 200 μg BV, five patients 300 μg BV, and two patients who had a Vesputa venom allergy, were treated with 200 μg VV.

The elevated maintenance dose was tolerated without any systemic side effects by all omalizumab patients ($p<0.001$ vs. controls, Fisher's exact test). After the maintenance dose of VIT had been reached, omalizumab was continued every 4 weeks up to 6 months. After the discontinuation of the omalizumab therapy, we observed a persisting tolerance of VIT. Average follow-up time was 5.8 years (IQR 2.7-8.6 years). 8 patients had sting challenge tests and none of the patients developed systemic reactions.

Two patients (Nr. 1 and 2) with a double VIT had had systemic side effects to both maintenance VITs, and had managed themselves to receive a pre-treatment with omalizumab. After that, no side effects to an elevated dose of the respective venom occurred; the sting challenge by the respective insect was tolerated well. The other four patients with double VIT neither experienced side effects to the complementary treatment, nor to complementary sting challenges with the culprit insect.

The majority of patients were candidates for a prolonged or even lifelong VIT, and were tolerating treatment well (two patients for more than 9 years). It was only in one patient with mastocytosis (Nr. 5) that systemic allergic reactions due to VIT occurred about two years after VIT tolerance had been established (including a tolerated sting challenge). This course of events made the patient think about stopping treatment. This patient had had several field stings, which initially had been tolerated and had then induced a moderate SAR (sensation of heat, nausea, dizziness) before systemic allergic reactions due to VIT recurred.

Basophil activation test was performed in three patients before VIT was resumed, and after an omalizumab pretreatment. Reactivity of peripheral blood leucocytes stimulated by the respective relevant venom declined after the first two injections of omalizumab (Fig. 1). Basophil reactivity increased again with prolonged injection intervals (Patient Nr. 1).

Discussion

Key finding of our study was that, if combined with a high dose venom maintenance therapy, a temporary omalizumab therapy was highly effective. None of the control patients who had experienced severe side effects of VIT, and for whom omalizumab was not available, could continue VIT. In contrast, all patients who had had the combination therapy achieved a permanent tolerance of maintenance VIT. After stopping omalizumab, tolerance of VIT persisted and a sting challenge test was tolerated in all tested patients. There was only one patient who again developed side effects due to VIT after treatment had been uneventful for two years. This patient was suffering from mastocytosis and had probably been re-sensitized by repeated field stings.

Up to now there is no standardized procedure how to continue safely VIT in patients with repeated moderate to severe SAR during VIT. Side effects of VIT are predictors for treatment failure (2). Furthermore, if SARs repeatedly occur during ambulatory care, patient compliance will be endangered. Moreover, the treating physician cannot always manage repeated anaphylactic reactions in the out-patient setting. Therefore, it is of utmost importance to establish a treatment tolerance.

Several significant risk factors for side effects during VIT cannot be modified, such as type of venom allergy or presence of a mast cell disease. To reduce the frequency of SARs during VIT in high risk patients, several strategies may be considered such as a pre-treatment with antihistamines (9, 10, 14) or attempts to increase the venom dose above standard levels (15). Effectiveness of antihistamines, however, is controversial and may depend on the specific type of drug (of which some have meanwhile been withdrawn from many markets worldwide). Increasing the venom dose in patients who have had SARs during standard VIT is demanding, tedious and often not possible because of the great procedural effort.

Two aspects formed the rationale of our combination therapy. First, our hypothesis was that repeated side effects due to standard immunotherapy indicate treatment failure, and that a successful immunotherapy might require the administration of a higher allergen dose. The effective venom dose may differ between individuals (possibly depending on the individual allergen recognition pattern); for many patients the standard venom dose of 100 µg may represent an under-dosing (mainly for bee venom). Second, there is a significant need to limit the duration of omalizumab treatment. Depending of the body weight and total IgE, the yearly costs of omalizumab are estimated to range between 7 000 and more than 13 000 €. Some patients may have to finance the omalizumab therapy themselves because several German health insurance companies do refuse coverage of an off-label omalizumab treatment. Even if a company does not do so, they still will just reimburse omalizumab costs, if the off-label prescription of the drug is strictly limited in time.

Our findings suggest that a temporary treatment with omalizumab is feasible allowing patients to safely reach a higher venom maintenance dose. Thereby, a permanent protection may finally be established.

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Omalizumab lowers free serum IgE and decrease FcεRI expression on basophils (16). This pharmacological action suggests that omalizumab may also prevent anaphylactic reactions. Up to now, however, omalizumab has only been approved for the treatment of severe allergic asthma and urticaria. Controlled large-scale studies in the field of immunotherapy are currently missing.

Several small pilot studies have been published in which omalizumab was given to patients with a food allergy (17, 18, 19). The main focus of these studies was the oral induction of tolerance (OIT) to food. In 14 children with cow milk or hen`s egg allergy, OIT combined with an omalizumab treatment led to a tolerance of the respective food (17). However, after stopping omalizumab clinical symptoms re-appeared in approximately half of the patients. These observations suggest that an anti-IgE-treatment may be only stopped safely, if the causative treatment is intrinsically effective.

An anti-IgE-treatment was also successfully used in combination with pollen immunotherapy; patients receiving such a regimen showed fewer adverse events compared with those receiving immunotherapy alone (20). The first case report of a combined omalizumab and Hymenoptera venom immunotherapy was published in 2005 (21). The one-time application of omalizumab had been combined with an ultra-rush immunotherapy protocol. This patient had initially tolerated honey bee VIT well, but then experienced a SAR when receiving a maintenance dose approximately one year after the start of VIT. This therapeutic failure was probably induced by an infection.

Meanwhile, a number case reports have been published that report the use of omalizumab in Hymenoptera venom allergic patients on VIT (11, 21-26). Treatment protocols using omalizumab in patients not tolerating VIT vary widely, and a standard regimen is not yet available; corresponding outcomes are inconsistent. In individual patients pre-treatment did not prevent systemic allergic reactions (23). In some patients omalizumab was found to prevent side effects of VIT. This prevention, however, required an ongoing omalizumab therapy (24). If the omalizumab dose was reduced, systemic reactions promptly recurred (11, 25).

Nevertheless, several patients tolerated VIT after restarting therapy, **and** continued to tolerate treatment after the anti-IgE-treatment had been stopped (12, 21, 22, 26). It remains unclear how long, how often, and at which dose the anti-IgE-antibody must be administered, to establish a persistent tolerance of VIT.

Our institutional omalizumab schedule was similar to that used in a study of ragweed pollen immunotherapy [20]. In this placebo-controlled trial omalizumab was begun 9 weeks before starting the immunotherapy, and was continued for 12 weeks along with the immunotherapy. Compared to immunotherapy alone this approach significantly reduced the overall frequency of adverse events, with a 5-fold reduction in the risk of anaphylaxis.

Up to now there were no data on whether patients are sufficiently protected from stinging anaphylaxis after the omalizumab therapy had been discontinued. Our observations suggest that this will be the case if an omalizumab therapy is combined with a high maintenance dose. There is only one case report presenting a patient who had received the same type of treatment protocol and who had developed a mild SAR after a sting exposure (26).

Limitations of the study: Our observational case series represents a single center study. Therefore, results may not be representative of a wide population of patients allergic to insect venom. As there are no accepted guidelines for the duration, the frequency and the dosage of omalizumab therapy in allergic patients, our omalizumab treatment schedule is arbitrary, and may not be the optimal or most cost-effective regime. . Furthermore, this was a retrospective analysis of data of which some had been generated over ten years ago. Some antiallergic therapeutic concepts have changed since then. Since we did not combine a temporary omalizumab therapy with a standard maintenance venom dose, we do not know whether omalizumab alone would have been as effective as the combination therapy.

In conclusion we feel that that our case series provides sufficient evidence to recommend a temporary use of omalizumab in selected patients in whom VIT would otherwise have to be discontinued. The time-dose schedule of omalizumab in combination with an elevated maintenance dose of VIT was safe and effective, even after stopping the anti-IgE-antibody therapy.

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Table 1

Classification of systemic allergic reactions according to Ring and Meßmer (13)

Classification	Symptoms
grade I	generalized skin symptoms (e.g. flush, generalized urticaria, angioedema)
grade II	mild to moderate pulmonary, cardiovascular, and/or gastro-intestinal symptoms
grade III	anaphylactic shock, loss of consciousness
grade IV	cardiac arrest, apnea

Table 2: Schedules and venom doses (μg) for the build-up of venom immunotherapy with an elevated maintenance dose (200 μg)

Days indicated with (*) only for patients with an indented maintenance of 300 μg venom

a) rush

Rush		
Day	Interval between injections (min)	Dose (μg)
1	90	0.02
	90	0.04
	90	0.08
	90	0.2
2	90	0,4
	90	0,8
	90	2
	90	4
3	90	8
	90	10
	90	20
	90	40
4	90	60
	90	80
	90	100
5	20	100
	20	30
6	20	20
	20	150
7*	20	30
	20	20
8*	20	250
	20	30
		20

b) ultra-rush

Ultra-Rush		
Day	Interval between injections (min)	Dose (μg)
1	30	0.01
	30	0.1
	30	1
	30	10
	30	20
	30	40
	30	80
2	20	100
	20	30
	20	20
3	20	150
	20	30
	20	20
4*	20	200
	20	30
	20	20
5*	20	250
	20	30
	20	20

Table 3 Characteristics of omalizumab patients

Case #	1	2	3	4	5	6	7	8	9	10
Gender	m	m	f	f	m	m	f	f	m	f
Age (years) ¹	32	39	29	34	34	53	49	53	65	41
Severity grade (SG) ² of sting reaction prior to VIT	SG III	SG III	SG III	SG III	SG III	SG II	SG III	SG III	SG III	SG III
Baseline serum tryptase concentration (µg/l)	7.6	21.2	3.0	15.5	127.0	6.7	6.4	18.6	43.1	14.1
Type of mastocytosis ³	Ø	ISM	Ø	Ø	ISM	Ø	Ø	ISM	ISM	MIS
Type of VIT ⁴	B-VIT and V-VIT	B-VIT and V-VIT	B-VIT	B-VIT	B-VIT and V-VIT	B-VIT and V-VIT	B-VIT	B-VIT and V-VIT	V-VIT	B-VIT and V-VIT
Type of therapy causing side effects ⁴	B-VIT	V-VIT	B-VIT	B-VIT	B-VIT	B-VIT	B-VIT	B-VIT	V-VIT	B-VIT
Maintenance dose (µg) at which side effects occurred	200	100	100	100	200	100	100	200	100	200
Duration of VIT (weeks) until the occurrence of side effects ⁵	17	5	1	22	90	1	4	54	2	82
Possible cause of side effects	SAR to sting challenge	?	?	after vaccination	SAR to sting challenge	?	?	after infection	?	allergic rhinitis and asthma
Number and severity grade (SG) ² of SAR ⁷ due to VIT	2 x SG II	2 x SG II	3 x SG II	1 x SG III 3 x SG II	2 x SG II	1 x SG III >3 x SG II	1 x SG II 2 x SG I	SG II 3 x SG I-II	2x SG II >5x SG I	1 x SG III >5 x SG I
Attempts to manage side effects										

Dose reduction	+	+	+	+	+	+	+	+	+	+
Antihistamines	+	+	+	+	+	+	+	+	+	+
Other			corticosteroids						Corticosteroids, switch from aqueous to depot extract	
Duration of omalizumab treatment (weeks)	21	23	21	15	13	26	26	27	36	21
Finally tolerated venom dose (µg)	300	200	200	200	300	300	300	300	200	200
Interval between discontinuation of omalizumab and sting challenge (months)	6	27	10	39	13	14	9	n.a. ⁶	n.a. ⁶	18
Outcome of sting challenge	Ø ⁸	Ø ⁸	Ø ⁸	Ø ⁸	Ø ⁸	Ø ⁸	Ø ⁸	n.a. ⁶	n.a. ⁶	Ø ⁸
Duration (years) of VIT tolerance after stopping omalizumab	9.9	9.3	8.3	6.5	1.9*	3.9	5.8	2,1	2.9	5.7

1, age at first visit for diagnosis and treatment of the respective venom allergy; 2, SG, severity grade of sting reaction prior to VIT (according to Ring and Messmer); 3, type of mastocytosis: Ø: no mastocytosis; ISM, indolent systemic mastocytosis; MIS, mastocytosis in the skin (bone marrow biopsy not done); 4, B-VIT, bee VIT; V-VIT, Vespula VIT; 5, interval between the establishment of the maintenance dose and the first onset of repeated systemic allergic reactions (weeks); 6, n.a., not available; 7. SAR, systemic allergic reaction; 8, Ø, no systemic reaction.

* Systemic allergic reactions due to VIT recurred after the patient had experienced several field stings and had developed a common cold. As a consequence, VIT was stopped by the patient.

Table 4 Characteristics of control patients

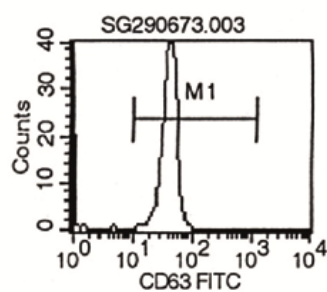
Case #	11	12	13	14	15
Gender	m	m	f	f	f
Age (years) ¹	43	49	57	39	51
Severity grade (SG) ² of sting reaction prior to VIT	SG III	SG III	SG IV	SG III	SG III
Baseline serum tryptase concentration (µg/l)	79.0	19.3	21.8	12.1	25.0
Type of mastocytosis ³	ASM	MIS	ISM	CM	ISM
Type of VIT ⁴	B-VIT	B-VIT	B- and V-VIT	B- and V-VIT	B-VIT
Type of therapy ⁴ causing side effects	B-VIT	B-VIT	B-VIT	B- and V-VIT	B-VIT
Maintenance dose (µg) at which side effects occurred	200	100	200	200 B-VIT 100 V-VIT	200
Duration of VIT (weeks) until the occurrence of side effects ⁵	8	16	64	12 (B-VIT) 28 (V-VIT)	4
Possible cause of side effects	?	?	SAR at bee sting challenge	varying (e.g., premenstrual, infection)	common cold
Number and severity grade (SG) ² of SAR ⁶ due to VIT	> 20 (SG I-III)	> 10 (SG I-II)	> 5 (SG III)	> 15 (SG I-II)	2 (SG III)
Attempts to manage side effects					
Dose reduction	+	+	+	+	+
Antihistamines	+	+	+	+	+
other			oral cortico-steroids, PUVA ⁷		

Interval (months) between the beginning and the end of VIT	21	21	26	63	2
Severity grade (SG) ² of a field sting reaction after treatment stop	SG III	n.a.	n.a. ⁸	n.a. ⁸	n.a. ⁸

1, age at first visit for diagnosis and treatment of the respective venom allergy; 2, SG, severity grade of sting reaction prior to VIT (according to Ring and Messmer); 3, type of mastocytosis: CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; ASM, aggressive mastocytosis; MIS, mastocytosis in the skin (bone marrow biopsy not done); 4, B-VIT, bee VIT; V-VIT, vespula VIT; 5, interval between the establishment of the maintenance dose and the first onset of repeated systemic allergic reactions (weeks); 6, SAR, systemic allergic reaction; 7, PUVA, oral psoralens and UVA; 8, n.a., not available.

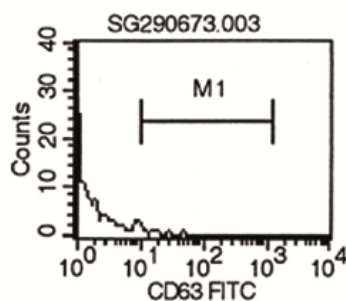
Patient 1:

Before omalizumab initiation



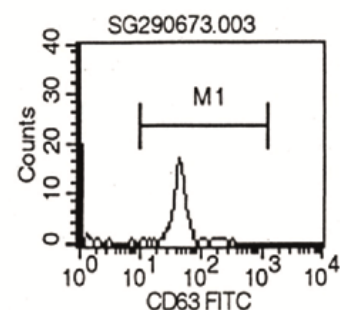
84.1% activation by BV

Day 19 after start of omalizumab



4.6 % activation by BV

**3 month after start of
omalizumab and
2 months after restart of VIT**



26.2% activation by BV